



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/091,605	06/16/1998	TRACY L. BORTS	X-9872	5126

7590 04/21/2003
ELI LILLY AND COMPANY
LILLY CORPORATE CENTER
DROP CODE 1104
INDIANAPOLIS, IN 46285

EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	2d

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/091,605

Applicant(s)

BORTS ET AL.

Examiner

Ram R. Shukla

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 6-17-02.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 35-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 35-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14.

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Shukla, whereas any inquiries relating to formal matters should be directed to Ms. Tabb, Patent Analyst. The phone numbers for Examiner Shukla and Patent Analyst Tabb are provided at the end of this office action.
2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-19-00 has been entered.
3. Claims 19-34 have been cancelled.
4. Claims 35-60 have been entered.
5. The 1.132 declaration by Anne Reifel Miller has been considered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
7. Claim 46-48, 56-58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 59 is directed to a gene therapy method of inducing insulin expression in a mammal by introducing an expression vector into the mammal. However, the claimed invention is not enabled because the art of gene

Art Unit: 1632

therapy at the time of the invention was unpredictable and the specification as filed does not provide sufficient guidance as to how an artisan of skill would have practiced the claimed invention without undue experimentation as discussed below. While progress has been made in recent years for *in vivo* gene transfer, vectors available continue to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Deonarain (1998) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art, which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (published in 1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242). Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted, "However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and

some efficacy has been determined in animals models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animal model is extended to a human subject.

The specification fails to teach one of skill in the art how to overcome the unpredictability for vector design and function such that efficient gene transfer is achieved by any mode of delivery. The specification fails to teach specific vectors, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

Regarding claims 46-48 and 56-58, it is noted that the application discloses several vectors that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

The specification discloses isolating vectors pLP53-tLB from bacteria deposited to NRRL, however, the specification does not teach what is the structure of the vector etc. Likewise the structure of other parent vectors is not described. Accordingly, an artisan would not know how to make and use the vectors claimed in the vectors of claims 46-48 and 56-58. It is unclear whether these vectors of claims 46-48 and 56-58 are known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth

in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 35-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is vague and indefinite because the metes and bounds of the term "mammalian origin" are not clear.

Claim 35 is vague and indefinite because the metes and bounds of the term "immunologically masked" are not clear.

Claim 36 is indefinite because it uses an improper Markush group. It is noted that the claim recites a group consisting of, however it also recites a or b. Therefore, it is unclear as to what are species of the group.

Claim 59 is vague and indefinite because it is unclear as to what is meant by the phrase "when incorporated into a cell".

Claim 60 is vague and indefinite because it recites the term "expressed in the introduced cells". It is unclear whether the expressed protein is secreted out of the cells or not, how will the insulin act in regulating glucose level.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 35-44, 49-55 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selden et al (US 6,048,724, 4-11-00, effective filing date 11-5-1991) in view of Pakzaban et al (Neuroscience 65:983-996, 1995).

Selden et al teaches a method of producing clonal cell strains that express GLP-1 (see the entire document). The art teaches human fibroblast cells that are transfected with an expression vector that encodes GLP-1 (17-37) (see example 11). The example also teaches transplanting cells in a mouse. Claims 1-3 are drawn to method of producing a clonal cell that expresses exogenous DNA encoding GLP-1. It is noted that while the art does not teach the sequence as recited in the claims, the sequence used by the art is 7-37 of GLP-1 as used by the instant

Art Unit: 1632

specification. The art does not teach mammalian cells expressing GLP-1 that are immunologically masked.

Pakzaban et al teaches that masking of donor MHC class I by F(ab')₂ treatment resulted in enhanced survival of xenotransplants.

At the time of the invention an artisan of skill would have been motivated to modify the method of Selden et al by treating the cells expressing GLP-1 with F(ab')₂ before transplanting them in a mouse with a reasonable expectation of success. An artisan would have been motivated to immunologically mask the cells being used for transplantation because such would have allowed immunoprotection of the transplanted cells.

12. Claims 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selden et al (US 6,048,724, 4-11-00, effective filing date 11-5-1991) and Pakazaban et al (Neuroscience 65:983-996, 1995) as applied to claims 35-44 and 49-55 above, and further in view of Gromada et al (FEBS LETTERS 1995, 373:182-186).

Selden et al teaches a method of producing clonal cell strains that express GLP-1 (see the entire document). The art teaches human fibroblast cells that are transfected with an expression vector that encodes GLP-1 (17-37) (see example 11). The example also teaches transplanting cells in a mouse. Claims 1-3 are drawn to method of producing a clonal cell that expresses exogenous DNA encoding GLP-1. It is noted that while the art does not teach the sequence as recited in the claims, the sequence used by the art is 7-37 of GLP-1 as used by the instant specification. The art does not teach mammalian cells expressing GLP-1 that are immunologically masked, wherein the mammalian cells are human embryonic kidney cells.

Pakzaban et al teaches that masking of donor MHC class I by F(ab')₂ treatment resulted in enhanced survival of xenotransplants.

Gromada et al teaches stimulation of GLP-1 receptor in human embryonic kidney cells 293 cells for studying the actions of GLP-1.

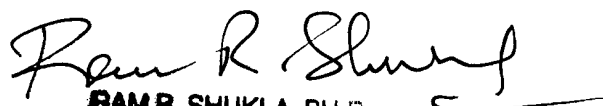
Art Unit: 1632

At the time of the invention an artisan of skill would have been motivated to modify the method of Selden et al by introducing the GLP-1 expression vector in 293 cells and then treat the cells expressing GLP-1 with F(ab')₂ before transplanting them in a mouse with a reasonable expectation of success. An artisan would have been motivated to make 293 cells producing GLP-1 because these cells are very common cell line used in experimentation and an artisan would have immunologically mask the cells before transplantation because such would have allowed immunuprotection of the transplanted cells and this would have allowed to determine whether different cells types have different effects when transplanted in a mammal.

13. Applicants' arguments and remarks regarding the previous office action are moot in view of the new grounds of rejection.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.


RAM R. SHUKLA, PH.D.
PATENT EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632